The impact of obesity on the cellular and molecular pathophysiology of COVID-19

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Emerging evidence reveals a strong association between COVID-19 and obesity in terms of disease severity, need for hospitalisation and risk of mortality. In this review, we discuss cellular and molecular mechanisms potentially contributing to the pathophysiology of COVID-19 in obese patients. Understanding the relationship between COVID-19 and obesity is pertinent for the clinical management of these patients.

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In December 2019, the World Health Organization (WHO) was informed of an increasing number of pneumonia cases observed in Wuhan City, China.[1] The disease is caused by the pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[2] and has since been termed coronavirus disease 2019 (COVID-19).[1] COVID-19 was declared a global pandemic,[1] with ~64 million cases and more than 1.4 million deaths reported to date.[3]

There is currently no vaccine or cure for COVID-19. Current recommendations aim to limit viral spread by using non-pharmacological interventions such as maintaining social distancing, wearing protective face masks, hand washing, sanitisation and where necessary, self-isolation following a positive diagnosis or exposure to a SARS-CoV-2-infected person. Symptomatic patients and those presenting with acute respiratory infections may require supplemental oxygen, corticosteroids (dexamethasone and others) and systemic anticoagulation. Attempts have been made to reduce viral load using oseltamivir, normally used to treat influenza type A and B, and remdesivir, a repurposed drug developed for Ebola. Treatments aimed at reducing the impact of the cytokine release syndrome (CRS) or cytokine storm include tocilizumab, an anti-IL-6 receptor monoclonal antibody.[4,5] Clinical trials are underway to determine the effects of convalescent plasma from patients with high titres of SARS-CoV-2, administered within 72 hours of diagnosis,[4] and the data to date are equivocal.

Disease severity is greater in some patients than in others. Most COVID-19 patients are asymptomatic or exhibit mild to moderate disease. A minority exhibit severe complications including acute respiratory distress syndrome and multiple organ failure, requiring hospitalisation with supplemental oxygen and assisted ventilation.[6-8] Older people, men and those with underlying conditions are at higher risk of severe illness. Risk factors for severe illness and death include hypertension, cardiovascular disease, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD), cancer and obesity.[9-12]

Selection criteria

Relevant literature was retrieved from PubMed and Google Scholar using the key words 'COVID-19 and comorbidities', 'obesity and COVID-19', 'obesity and ACE2', 'obesity and immune response' and 'obesity and cellular and molecular mechanisms'. From these sources, we evaluated and selected articles on the epidemiology, and cellular and molecular mechanisms of COVID-19 in the context of obesity. This is not an exhaustive systematic review or a meta-analysis but rather a descriptive review in an ever-changing field of some of the key pathogenetic mechanisms to have emerged in a disease whose existence we have known about for less than a year.

Obesity and COVID-19

Obesity is a global pandemic and has almost tripled in prevalence since the 1970s. The WHO defines obesity as the accumulation of fat, which can negatively affect health. Overweight people have a body mass index (BMI) >25 and a BMI ≥30 is defined as obesity. Obesity affected more than 650 million people globally in 2016 and is a risk factor for cardiovascular disease, type 2 diabetes mellitus, kidney disease and cancer. An increase in BMI and adiposity also increases the risk of contracting infections.[14] Developed countries have a higher prevalence of obesity, but urbanisation and globalisation have led to a surge of obesity in developing countries.[15]

COVID-19 patients with obesity, and mostly males, present with severe disease. They often require hospitalisation and mechanical ventilation, are admitted to the intensive care unit (ICU) and have a higher probability of mortality.[9,16-21] Data from Africa are lacking, but global trends suggest that obesity is also a risk factor for more severe COVID-19 disease in African populations.

The strong association between COVID-19 and obesity is not well understood. In this article, we review the potential cellular and molecular mechanisms contributing to severe COVID-19 in obese patients.

The pathophysiology of obesity and COVID-19

Immunopathogenesis

Obesity in the general population is associated with a depressed immune system and chronic low-grade inflammation characterised by an increase in adipokines and pro-inflammatory cytokines.[22] When obese patients are infected with COVID-19, the two pathologies appear to act in concert to further impair immune function and elicit a more severe inflammatory response, resulting in more severe COVID-19 disease.[21,23,24] The CRS, an uncontrolled and excessive production of pro-inflammatory cytokines has been observed in critically ill COVID-19 patients.[25-27] Various cytokines are released, including interleukin-1 (IL-1), IL-6 and IL-10, as well as

growth factors, colony-stimulating factors, interferons, macrophage inflammatory proteins and tumour necrosis factor alpha (TNFα). Most studies have found significantly increased levels of IL-6 and TNFα in COVID-19 patients.[25,26] These pro-inflammatory cytokines increase vascular permeability, which causes blood cells and fluid to enter alveoli, producing symptoms such as dyspnoea.[28] The CRS is believed to be responsible for the presentation of acute respiratory distress syndrome (ARDS) and multi-organ failure in some COVID-19 patients.[25,26]

To respond effectively against viral infections, our immune systems rely on optimally functioning T cells. Low T cell counts are a known risk factor and predictor of poor prognosis and mortality in COVID-19 patients.[29,30] In Wuhan, China, patients with severe COVID-19 had significantly fewer cytotoxic and helper T cells.[30] Defective T cell-mediated immune responses have also been observed in obese patients, who are more likely to be hospitalised if they acquire respiratory infections.[31]

Immune dysregulation in obese people may also include reduced antiviral cytokines, diminished natural killer cell activity and dysfunctional macrophages.[32-34] Impaired activation and functioning of $CD4^+$ and $CD8^+$ T cells have been observed in overweight and obese individuals who were infected with the H1N1 virus, which may have contributed to disease severity and mortality.[35] When infected with influenza A/Puerto Rico/8/34 (A/PR8), obese mice showed reduced expression of interferon alpha (INFα) and INFβ in the early stages of infection and this remained low throughout the infection.[32] These mice had diminished natural killer cell proliferation and activity in the lungs.[32] Other forms of immune dysregulation observed in obese mice infected with influenza included reduced expression of monocyte chemoattractant protein 1 (MCP-1), regulated upon activation normal T cell expressed and secreted (RANTES) and a delayed expression of the essential cytokines, TNFα and IL6.[32] Obese people who had severe H1N1 disease had reduced macrophage activation and cytotoxic activity.[33] It is possible that the dysfunction in the innate immune system of obese patients may also contribute to the severity of COVID-19 symptoms.

Another link between the severity of COVID-19 disease and obesity may be the chronic production of leptin due to an increased number of adipocytes.[36,37] The immune response becomes dysregulated when T cells and natural killer cells become resistant to leptin.[38] High levels of leptin were associated with disease severity and mortality in obese mice infected with H1N1.[39] Leptin also increases the production of leukotrienes by alveolar macrophages and may ultimately cause pulmonary inflammation.[40]

Adipose tissue, obesity and receptors for SARS-CoV-2

Adipose tissue expresses receptors such as angiotensin-converting enzyme-2 (ACE2) and dipeptidyl peptidase 4 (DPP4), which facilitate the entry of SARS-CoV-2 into human cells and increase viral load.[41]

In the lungs, SARS-CoV-2 binds to the ACE2 receptor, upregulating the expression of ACE2 and damaging alveolar cells.[42] The ACE2 receptor is overexpressed in the adipose tissue of COVID-19 patients.[43,44] Since obese people have more adipose tissue, they are expected to have more ACE2 receptors. ACE2 receptors are expressed in monocytes and macrophages,[45] which are also more prevalent in the adipose tissue of obese people.[46,47] It is therefore likely that adipose tissue acts as a viral reservoir and possibly allows for inter-organ transmission.[43,44] When cells bearing ACE2 receptors are infected, their immunomodulatory activity is impaired and they produce proinflammatory factors which contribute to inflammation.[48] Monocytes expressing ACE2 are involved in regulating blood vessel homeostasis through the renin-angiotensin-aldosterone system (RAAS). When SARS-CoV-2 activates ACE2 on monocytes, this disturbs the RAAS, resulting in acute coronary syndrome.[49]

SARS-CoV-2 may also enter cells of the respiratory tract via DPP4, a receptor used by the middle east respiratory syndrome coronavirus (MERS-CoV)[50] and also known as cluster of differentiation 26 (CD26).[51,52] DPP4 is a membrane-bound glycoprotein with multiple functions including glucose and insulin metabolism and immune regulation.[53] DPP4 was identified as a potential SARS-CoV-2 receptor using bioinformatic and protein-docking prediction tools.[50] In obese people, DPP4 is overexpressed in visceral adipose tissue and the liver.[54,55] DPP4 has immunomodulatory activity, activating and causing the proliferation of T cells and production of cytokines, and potentially contributing to and exacerbating hyperinflammation.[54-56]

Obesity-associated comorbidities and SARS-CoV-2

Obesity is associated with various comorbidities that may contribute to the severity of COVID-19. Obese people are disproportionately affected by hypertension, type 2 diabetes, pulmonary diseases and cancer,[57,58] which have also been identified as risk factors for severe COVID-19.[59]

Obesity affects the functioning of the respiratory system and is associated with several respiratory conditions including sleep apnoea, asthma, obesity hypoventilation syndrome, COPD, pulmonary hypertension, aspiration pneumonia, pulmonary embolism (PE),[14,60,61] and respiratory infection.[31] Obese people are more likely to accumulate adipose tissue around the upper airways, chest wall and abdomen, impairing the mechanics of the lungs.[62] Obesity is also a risk factor for venous thromboembolic diseases, which include deep vein thrombosis and PE. Recent comparisons suggest that overweight or obese COVID-19 patients are more prone to developing PE, possibly due to the presence of excess adipose tissue.[63,64] The risk of thrombosis increases with increasing BMI and waist circumference. Thromboembolic disease is caused by chronic inflammation, adipokines, an increase in coagulation activity, a decrease in fibrinolytic activity and procoagulant microparticles.[65]

Obesity is also associated with the development and progression of chronic kidney disease and end-stage renal disease.[66] Pre-existing or underlying kidney disease were identified as risk factors for severe COVID-19 (83.93%) and related mortality (53.33%) in a recent meta-analysis.[67]

Obesity and COVID-19 in South Africa

The prevalence of obesity in South Africa (SA) is increasing rapidly, with at least 68% of women and 31% of men reported as being either overweight or obese in 2016.[68] In addition, 13.5% of school-going children between the ages of 6 and 14 years were reported to be overweight or obese, which is above the 10% global prevalence.[69] In a country with high rates of unemployment, poverty and infectious diseases such as HIV and tuberculosis, obesity and its associated comorbidities have a negative impact on the livelihoods of many people. The disease burden leads to an increase in healthcare costs at both the individual level and that of the healthcare system.[70]

Obesity in SA is driven by high levels of poverty, unemployment and low income.[71] In the first quarter of 2020, Statistics South Africa (Stats SA) reported that the unemployment rate was 30.1% and ~40 000 jobs had been shed across various sectors.[72] In addition to this, 35.1 million SA adults live below the upper-bound poverty line of ZAR1 227 per month.[73, 74] People from low-income households tend to buy less expensive foods which are gastronomically filling and energy-dense, but rich in starch, fat and sugar.[71] The surge in obesity

in developing countries such as SA is associated with urbanisation and globalisation,[15] and the increased intake of high-calorie fast foods and the consumption of sugar-sweetened beverages.[15,71] Insufficient physical activity and a sedentary lifestyle are also complicit in weight gain and obesity.[71]

Many countries have implemented strategies that limit physical activity to curb the spread of COVID-19, which may have increased the prevalence of obesity. On the 26 March 2020, SA went into an official lockdown due to the COVID-19 pandemic. Restrictions included staying indoors, working remotely, closing of gyms and limited outdoor exercise.[75] In response, many people changed their eating patterns and switched to a more sedentary lifestyle, which created an obesogenic environment. Recently the lockdown restrictions were eased to stimulate economic activity[75] and places selling fast-food were first to open, with fatty and processed foods becoming easily available to the public. Due to a fear of contracting COVID-19, many SA citizens abandoned or froze their gym memberships and have reduced their levels of physical activity. This could exacerbate the rising prevalence of obesity in SA, further increasing the risk of severe COVID-19.

Implications of obesity in the COVID-19 pandemic

Obese patients generally respond poorly to vaccinations and antiviral treatments.[76] This is most likely due to poor antibody responses or poor absorption of vaccines due to increased adiposity.[38] With several countries in the process of developing COVID-19 vaccines, there is a concern that vaccines may not be effective in obese individuals.

Obese COVID-19 patients also seem to be more contagious than lean patients,[77,78] possibly due to the fact that obesity influences the viral life cycle and increases virus shedding. Viral load is also likely to be greater because of the subdued or delayed immune response, as was seen in the H1N1 pandemic.[79,80] Healthcare professionals should therefore be cognisant of the consequences of isolation procedures and make provision for the likelihood of an increase in an obesogenic environment.

The interplay between obesity and COVID-19 has placed an additional burden on healthcare systems globally. Obese patients have suffered disproportionately from COVID-19, requiring hospitalisation and ICU admission and have needed more resources such as ventilators.[9,16,18] In low-resource settings such as SA and particularly in rural areas, the interplay between COVID-19 and obesity could place a severe strain on the healthcare system. Globally, healthcare systems were overwhelmed by sudden peaks in cases, leaving hospitals ill-prepared in terms of resources. These observations highlight major challenges faced by healthcare systems as a consequence of the ongoing increase in the prevalence of obesity.

Conclusions

Obesity is an independent risk factor for severity and mortality in COVID-19. Obesity increases the need for hospitalisation and mechanical ventilation. In addition to chronic inflammation, obese individuals have defective innate and adaptive immune responses, which are the most plausible links between obesity and severe COVID-19. Increased expression of ACE2 and DPP4 in adipose tissue may increase viral load and drive disease severity. Curbing viral transmission via lockdown restrictions, social distancing and reduced physical activity may enable behaviour that encourages weight gain. The strong association between COVID-19 and obesity-related comorbidities highlights a need for healthcare systems to promote interventions that address non-communicable diseases, including routine health checks, the importance of nutrition and exercise.

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